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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,238	07/15/2005	Kathleen Freson	50304/091001	8603

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
07/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/542,238	FRESON ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-26* is/are pending in the application.

4a) Of the above claim(s) *16-20,22,25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,21,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/1/05, 4/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response received April 18, 2008 is acknowledged.

Applicant's election without traverse of the species of anti-PACAP antibodies as a PACAP inhibitor in the reply filed on April 18, 2008 is acknowledged.

Claims 16-20, and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 18, 2008.

Claims 25 and 26 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the restriction requirement mailed October 11, 2007.

Claims 14, 15, 21, 23, and 24 are under examination as they read on methods of treating thrombocytopenia by administering the PACAP inhibitor species of anti-PACAP antibodies.

Information Disclosure Statement

2. The IDS forms received 9/1/05 and 4/18/08 are acknowledged and have been considered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 14, 15, 21, 23, and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating

thrombocytopenia with antibodies that bind PACAP, does not reasonably provide enablement for methods of prevention or methods of treatment with the genus of all inhibitors of PACAP signaling. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has claimed methods of preventing and treating thrombocytopenia by administering inhibitors of PACAP signaling. A working example is provided wherein an antibody that binds the PACAP peptide is administered to mice. Mice receiving the antibody administration were observed to have circulating platelet levels that were greater than that observed in normal controls, and such mice recovered more quickly from chemically induced thrombocytopenia than normal counterparts. As such, it appears that administering an antibody that binds the PACAP peptide can induce the release of greater than normal levels of platelets from megakaryocytes, and that such a method would be beneficial in treating thrombocytopenic patients who have insufficient levels of platelets to support normal homeostasis. Thus, applicant's method appears to work by increasing platelet titers. Megakaryocyte maturation and platelet release are complex biological phenomena governed by a myriad of factors including cytokines and integrins (Takizawa et al., and Dhanjal et al.). To this field of endeavor, applicant has added PACAP signaling.

PACAP is a peptide that binds to a least 3 distinct receptors (see particularly page 3 of the specification and Table I of Sherwood et al.) One receptor (PACAPR) appears to only bind PACAP, while the other two receptors (VPAC1 and VPAC2) bind PACAP and VIP. VIP is an endogenous peptide that comprises a distinct amino acid sequence as compared to PACAP and is implicated in a wide variety of physiological responses (Sherwood et al., see particularly Figure 3, section A on pages 635-636, and section V beginning on page 639). Note that while both PACAP and VIP have been reported to have an array of diverse functions in the nervous, endocrine, cardiovascular, muscular and immune systems, there are differences in tissue distribution and receptor usage as described previously, and thus VIP and PACAP are not absolutely redundant and interchangeable in all physiological settings. The specification defines "PACAP

signaling" as encompassing binding of PACAP to PACAPR, VPAC1, and VPAC2, as well as VIP binding to VPAC1 and VPAC2. Thus it is clear that there are multiple signaling pathways that applicant has aggregated under the term "PACAP signaling". The specification demonstrates that by reducing the level of PACAP peptide by administering an antibody that binds PACAP, a rise in platelet titer can be observed. The specification does not indicate if this effect is due to lack of signaling by PACAPR, VPAC1, VPAC2, or some combination of said receptors. As such, which receptor(s) is/are important for the observed rise in platelet titers? Given that VPAC1 and VPAC2 are not specific for PACAP, signaling through these receptors can still occur via interactions with VIP. Given that multiple pathways are involved in PACAP signaling, it is clear that agents contemplated in the specification as "inhibitors of PACAP" cannot simultaneously block all the pathways. Even in the case of administering antibodies that bind the PACAP peptide, the VIP peptide is still able to interact with VPAC1 and VPAC2 to promote "PACAP signaling". Thus, while it is reasonable that PACAP signaling can be inhibited and thus thrombocytopenia can be treated, it does not appear that PACAP signaling can be completely blocked such that thrombocytopenia can be "prevented". It should be noted that page 10 of the instant specification indicates that "anti-PACAP antibodies" bind PACAP, VIP, or any functional derivative thereof. The specification does not demonstrate that anti-VIP antibodies are able to increase platelet titers, and given the structural, distributional and receptor differences between PACAP and VIP, it does not seem reasonable that antigen specificity can be considered completely interchangeable in the absence of additional data. Also, since the method is performed in a subject, the administered "anti-PACAP antibody" must be able to bind an endogenous peptide, such as PACAP. However, the definition of "anti-PACAP" encompasses antibodies that bind derivatives (such as non-naturally occurring molecules), yet said definition does not indicate that antibodies that bind derivatives must also be able to crossreact with native endogenous peptides. Thus, the full scope of "anti-PACAP" is not reasonably enabled. Further, while the specification discusses the terms "treatment" and "prevention" on page 11 of the instant specification, no guidance is given as to what level of efficacy is required for these terms. Thus, it

appears that the term "prevention" encompasses 100% efficacy in 100% of patents, a level of operability that is not reasonably supported by the examples of the instant specification.

Therefore, given the breadth of the claimed invention, the guidance and direction present in the instant specification, the nature of the working examples, and the teachings of the art, a skilled artisan would not be able to practice the breadth of applicant's claimed invention without first conducting additional unpredictable experimentation.

5. Claims 14, 15, 21, and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has claimed broad methods of administering inhibitors of "PACAP signaling". Dependent claim 21 recites a structurally and mechanistically diverse set of molecules that can be used to perform the instant claimed methods, including antisense, RNAi, small molecules, antibodies, and ribozymes without indicating any antigen or target specificity for the recited molecules. Dependent claim 15 recites that the inhibitor targets expressed PACAP, but recites no structure for the inhibitor itself.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412)

19 F. 3d 1559, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

The instant specification defines "PACAP signaling" on page 9 as involving the binding of two peptides, VIP and PACAP to three distinct receptors (PACAP, VPAC1, and VPAC2). The recited inhibitors of claim 21 are all structurally and therefore mechanistically diverse in their mechanism of action. Thus it is not reasonable to say that they comprise a shared structure that is correlated with the activity of PACAP signaling. Further, what molecule is being targeted by the antisense, RNAi, or antibody of the claim? Even if a target is specified, such as targeting expressed PACAP for example, it does not appear that the specification provides adequate written description to demonstrate that applicant was in possession of the recited genus at the time the application was filed. For example, applicant indicates that small molecule inhibitors can be obtained by screening combinatorial, natural and random peptide libraries (see particularly page 13). As such it is clear that the structure of said small molecules was

wholly unknown to applicant at the time the instant invention was filed since such screening assays were not performed and the possible starting materials literally include anything that can be thought of that can be run through a screening assay.

Thus, a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of inhibitors of PACAP signaling inhibitors at the time the instant invention was filed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 14, 15, 21, 23, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by DiCicco-Bloom et al. (US 2002/0182729A1, of record).

DiCicco-Bloom et al. disclose administering antibodies that bind PACAP to patients (see entire document, particularly paragraphs 28, 36-38, and 40).

It is noted that DiCicco et al. do not disclose that such an administration prevents or treats thrombocytopenia. However, the preamble of the instant claim does not recite that the patient to whom the inhibitor is administered has been diagnosed as having thrombocytopenia. The only positively recited method step is administering an inhibitor of PACAP signaling to a patient. DiCicco et al. teach such a method. Further, "prevention" can reasonably be interpreted to mean that the inhibitor is administered prior to a person developing thrombocytopenia. Since thrombocytopenia (low platelet count) is not desirable for any person, it is reasonable that one would wish to prevent thrombocytopenia from developing in all patients. Thus the patient population of the instant methods include all humans and are not limited to any particular preselected subset of humans. Note that since the same inhibitory agent is administered (i.e. antibodies that bind PACAP) in the prior art and the instant claims, any physiological response not disclosed by the prior art, such as its influence on platelet maturation and

thrombocytopenia, are inherent properties. Note that there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). As stated above, given that the positively recited administration steps are the same between the prior art and the instant claimed methods, the prior art methods anticipate the instant claimed invention.

8. No claims are allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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